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Steven F. Weinstock-
WOOD, PHILLIPS, KATZ, CLARK & MORTIMER
500 West Madison Street, Suite 3800
Chicago, IL 60661

EXAMINER	
KISHORE, GOLLAMUDI S	

ART UNIT	PAPER NUMBER
1612	

MAIL DATE	DELIVERY MODE
11/10/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/558,159	JAMIL ET AL.	
	Examiner	Art Unit	
	GOLLAMUDI S. KISHORE	1612	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 October 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-99* is/are pending in the application.

4a) Of the above claim(s) *3-9 and 42-99* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2 and 10-41* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *5-19-06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's election without traverse of Group I and drugs cytotoxic to tumor cells as the species in the reply filed on 10-23-09 is acknowledged.

Claims included in the prosecution are 1-2 and 10-41. Claims 29 and 30 are included in the prosecution since they recite some drugs which fall within the elected species category.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claims 12-13, 29, 35 and 41 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The terms, short and long in claims 12-13 are relative terms. Carbon chain length should be specified.

'including' renders claim 29 indefinite; it is unclear whether the limitation in parenthesis in claim 29 is indeed the limitation Similar is the case with claim 35.

It is unclear as to what '!' in claim 41 represents.

Claim Rejections - 35 USC § 102

> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

4. Claims 1-2, 19, 21, 24, 27 are rejected under 35 U.S.C. 102(b) as being anticipated by Saxon (Journal of Liposome Research, 1999).

Saxon discloses liposomes containing vincristine and mitoxantrone. The liposomes contain DSPC and cholesterol (abstract, Preparation of liposomes on page 510).

3. Claims 1-2, 10-13, 15-17, 21-22, 24, 27 are rejected under 35 U.S.C. 102(b) as being anticipated by Rahman (4,952,408).

Rahman discloses liposomal compositions containing cardiolipin. The anti-cancer agents include a combination of vinca alkaloids vincristine, vinblastine, and vindesine. The liposomes are negatively charged (abstract, col. 2, line 50 through col. 3, line 25 and claims).

> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

5. Claims 1-2, 17, 19-30, 35-37 are rejected under 35 U.S.C. 102(e) as being anticipated by Tardi (US 2003/0147945).

Tardi discloses liposomal formulations containing various combinations of anti-cancer drugs. The combinations include carboplatin: daunorubicin, cisplatin: Topotecan or Irinotecan, CPT-11: FUDR (Figures, 0081-0082; 0140; 0150-0160; 0170, Examples and claims).

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. Claims 10-17 and 19-30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Saxon cited above further in view of Rahman (4,952,408).

The teachings of Saxon have been discussed above. Saxon in addition suggests that drugs such as doxorubicin and vincristine are known to be used in combination therapy and when considering the use of combination therapies with liposomal anticancer agents several approaches can be defined. One such approach according to Saxon is the administration of one liposomal formulation containing more than one entrapped drug (page 508). Saxon also lacks the use of cardiolipin in the liposomes.

Rahman as pointed out above teaches liposomal formulations containing vinca alkaloids for cancer therapy.

To encapsulate vinca alkaloids along with other anti-cancer drugs such as mitoxantrone or doxorubicin would have been obvious to one of ordinary skill in the art with a reasonable expectation of success since Saxon teaches co encapsulation of vincristine and mitoxantrone in liposomes and suggestive of co-encapsulation of other agents within the liposomes. The use of cardiolipin in the liposomes of Saxon would have been obvious to one of ordinary skill in the art with a reasonable expectation of success since it is commonly used lipid in liposomes as taught by Rahman.

8. Claims 1-2, 17-30, 35-37 are rejected under 35 U.S.C. 103(a) as being unpatentable over Englom (British Journal of Cancer, 1999), Kano (Leukemia Research, 1993), Guichard (Biochemical Pharmacology, 1998) or Kuebler (Journal of interferon Research, 1990) in view of Saxon or Tardi cited above.

The teachings of Saxon and Tardi have been discussed above. Saxon in addition suggests that drugs such as doxorubicin and vincristine are known to be used in combination therapy and when considering the use of combination therapies with liposomal anticancer agents several approaches can be defined. One such approach according to Saxon is the administration of one liposomal formulation containing more than one entrapped drug (page 508). Tardi teaches a variety of anti-cancer drugs.

Englom teaches additive and supra-additive cytotoxicity of cisplatin-taxane combination in ovarian carcinoma cell lines (Summary).

Kano teaches synergistic effects of carboplatin in combination with cytosine arabinoside, mitoxantrone and cPT-11 (Irinotecan) and additive effects of carboplatin in combination with bleomycin, daunorubicin, etoposide and others (abstract).

Guichard discloses synergistic activity of 5-fluoracil and Irinotecan (abstract). In essence, these references teach the synergistic effect of drug combinations. What is lacking in these references is the teaching of the use of liposomes as carriers.

Kuebler teaches synergistic effects of vinblastine and recombinant interferon-beta on renal cell lines (abstract).

To encapsulate drug combinations taught by Englom, Kano, Guichard, Kuebler in liposomes would have been obvious to one of ordinary skill in the art with a reasonable

expectation of success since Saxon suggestive of co-encapsulation of other agents within the liposomes. The use of charged liposomes or neutral liposomes which are either unilamellar or multilamellar would have been obvious to one of ordinary skill in the art since these are routinely used in the delivery of drugs. Since it is well-known that the hydrophilic agents are added in the phospholipid hydrating medium and the hydrophobic agents are added in the lipid phase, encapsulation of the hydrophilic agents in the aqueous interior and the hydrophobic agents in the lipid bilayer would have been obvious to one of ordinary skill in the art.

9. Claims 10-36 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tardi (US 2003/0147945) in combination with Rahman (5,665,710).

The teachings of Tardi have been discussed above. What is lacking in Tardi is the teaching that the anti-tumor agent is antisense c-raf. Also lacking in Tardi is the teaching of the use of cardiolipin as the liposome forming lipid.

Rahman discloses the cytotoxicity of antisense c-raf and the liposomal incorporation of c-raf. The liposome forming lipids include cardiolipin, phosphatidic acid (negatively charged) and quaternary amine containing phospholipids. The liposomes further include cholesterol and tocopherol (abstract, col. 1, line 65 through col. 5, line 65; Examples).

The use of antisense c-raf oligonucleotide in the drug combination taught by Tardi and the inclusion of a targeting ligand with a reasonable expectation of success would have been obvious to one of ordinary skill in the art because of the effectiveness taught by Rahman. The inclusion of lipids such as cardiolipin and cholesterol would

have been obvious to one of ordinary skill in the art with a reasonable expectation of success since these are used in liposomes as taught by Rahman.

10. Claims 31-41 are rejected under 35 U.S.C. 103(a) as being unpatentable over 1) Saxon; 2) Saxon in view of Rahman 3. Englom (British Journal of Cancer, 1999), Kano (Leukemia Research, 1993), Guichard (Biochemical Pharmacology, 1998) or Kuebler (Journal of interferon Research, 1990) in view of Saxon or Tardi 4) Tardi (US 2003/0147945) all as set forth above, further in combination with Allen (6,316,024).

The teachings of Saxon, Rahman, Englom, Kano, Guichard, Kuebler and Tardi have been discussed above. What is lacking in these references is the teaching of a targeting ligand on the liposomes.

Allen while disclosing liposomal formulations containing anti-cancer agents including antisense nucleotides teaches that a variety of targeting ligands can be attached to the liposomes to target cells to specific cells (abstract, col. 2, line 56 through col. 3, line 14; col. 8, line 27 through col. 9, line 38; col. 10, line 56 through col. 11, line 50; examples and claims).

The use of a targeting ligand on the liposomes would have been obvious to one of ordinary skill in the art since the targeting ligands direct the liposomes to the targeted sites as taught by Allen.

11. Claims 31-36 and 38 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tardi (US 2003/0147945) in combination with Cheresh (US 2003/0092655).

The teachings of Tardi have been discussed above. What are lacking in Tardi are the teachings that the anti-tumor agent is antisense c-raf oligonucleotide and the presence of a targeting ligand on the liposomes.

Cheresh discloses that angiogenesis is a requirement for malignant tumor growth and the expression of a specific angiogenesis marker, the alpha, beta integrin is known to correlate with tumor grade. Therefore, Cheresh teaches liposome encapsulated mutant Raf genes and containing integrin antagonist as the targeting ligand (0029-0030; 0033, 0124, 0128, 0130-0131 and claims 27 and 43).

The use of antisense c-raf oligonucleotide in the drug combination taught by Tardi and the inclusion of a targeting ligand with a reasonable expectation of success would have been obvious to one of ordinary skill in the art because of the effectiveness taught by Cheresh.

The references of Kasid (6,126,965) and Rahman (5,560,923) are cited as interest.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to GOLLAMUDI S. KISHORE whose telephone number is (571)272-0598. The examiner can normally be reached on 6:30 AM- 4 PM, alternate Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Krass Frederick can be reached on (571) 272-0580. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Gollamudi S Kishore/
Primary Examiner, Art Unit 1612

GSK